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1 507 462

PATENT SPECIFICATION (11) 1 507 462

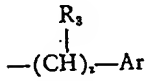
(21) Application No. 12572/74 (22) Filed 21 March 1974
(21) Application No. 35402/74 (22) Filed 12 Aug. 1974
(23) Complete Specification filed 10 March 1975
(44) Complete Specification published 12 April 1978
(51) INT CL² C07D 211/06; A61K 31/445; C07D 405/06, 409/06// C07C 103/46 (C07D 409/06, 211/58, 333/20)
(52) Index at acceptance C2

(19)

ERRATUM

SPECIFICATION No. 1,507,462

Page 2, line 1, *after* R_3 (second occurrence) *delete* an *insert* on
Page 4, line 1, *for* There *read* These
Page 9, TABLE 1, FORMULA 1, Column headed



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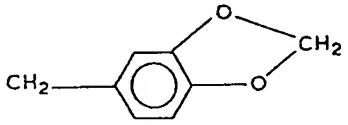

Page 12, line 38, *for* 14'- *read* -4'-
Page 16, line 5, *for* thioprene *read* thiophene

THE PATENT OFFICE
4th September, 1978

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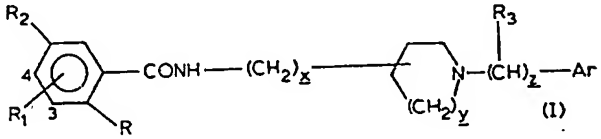

in which:

R is a C_1—C_6 alkoxy or C_2—C_6 alkenoxy group;

R_1 and R_2, which may be the same or different, are chosen from hydrogen (provided that R_1 and R_2 are not both hydrogen), halogen, sulphonamido, amino, (C_1—C_6)-alkyl- or di-(C_1—C_6)-alkylamino, alkylsulphonyl, mono- or dialkyl-sulphonamido or acylamino groups, the radical R_1 being positioned at the 3 or 4 position of the aromatic ring;

R_3 is hydrogen, or a C_1—C_6 alkyl or optionally substituted aryl group, provided that, where z is greater than 1,

SEE ERRATA SLIP ATTACHED

PATENT SPECIFICATION (11) 1 507 462

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(21) Application No. 12572/74 (22) Filed 21 March 1974
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(52) Index at acceptance
C2C 1494 1510 1532 200 213 215 220 226 227 22Y 246 247 250 251 253 254 25Y 280 281 282 28X 29X 29Y 30Y 311 313 316 31Y 321 32Y 338 339 341 342 34Y 351 355 364 365 366 367 368 36Y 385 396 440 455 45Y 510 51X 536 537 57Y 591 603 613 620 624 625 626 628 62X 634 63X 644 65X 660 662 668 670 680 682 695 697 699 69Y 71X 790 79Y KD KH KM KP KZ LH NG RE SF

(72) Inventors ROBERT GEOFFREY WILLIAM SPICKETT, ARMANDO VEGA NOVEROLA, JOSE PRIETO SOTO and JACINTO MORAGUES MAURI

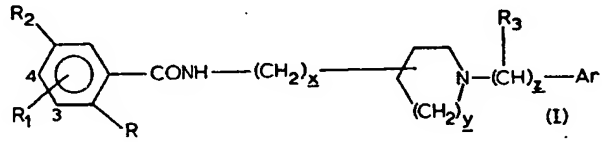
(54) N-HETEROCYCLIC SUBSTITUTED BENZAMIDES, METHODS FOR THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

(71) We, ANTONIO GALLARDO, S.A., a body corporate organised under the laws of Spain of Cardoner 68-74, Barcelona 12, Spain, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to N-heterocyclic substituted benzamides, methods for their preparation and compositions containing them.

The compounds of the invention have as one of their principal pharmacological properties the ability to antagonise the effects of dopamine or dopaminergic agents of endogenous or exogenous origin. They may be used for the treatment of nausea and vomiting resulting from gastro-intestinal disorders, congestive heart failure, post operative conditions, other gastrointestinal disorders such as dyspepsia, flatulance, bile regurgitations, hiatus hernia, peptic ulcer, reflux oesophagitis, gastritis, duodenitis and cholelithiasis, and a variety of conditions affecting the central nervous system such as acute and chronic psychoses, manical psychosis, schizophrenia, serious disturbances of behaviour and non-melancholic depressive state and migraine.

According to our invention, in its broadest aspect, we provide a compound corresponding to the general formula (I):



(I)

in which:

R is a C_1—C_6 alkoxy or C_2—C_6 alkenoxy group;

R_1 and R_2, which may be the same or different, are chosen from hydrogen (provided that R_1 and R_2 are not both hydrogen), halogen, sulphonamido, amino, (C_1—C_6)-alkyl- or di-(C_1—C_6)-alkylamino, alkylsulphonyl, mono- or dialkyl-sulphonamido or acylamino groups, the radical R_1 being positioned at the 3 or 4 position of the aromatic ring;

R_3 is hydrogen, or a C_1—C_6 alkyl or optionally substituted aryl group, provided that, where z is greater than 1,

SEE ERRATA SLIP ATTACHED

R_3 is hydrogen or two groups R_3 an adjacent C-atoms form a bond between the said C-atoms with any remaining groups R_3 being hydrogen;
Ar is an optionally substituted aryl, aroyl or single ring aromatic heterocyclic group;
x is 0 or 1;
y is 2 or 3; and
z is an integer of from 1 to 6,
or a pharmaceutically acceptable salt or N-oxide derivative thereof.

The acylamino group which may be present as the radical R_1 or R_2 or both may be represented by the formula: (R_4CONH), where R_4 is hydrogen, C_1—C_6 alkyl, mono-, di- or trisubstituted halogenoalkyl, an amino or substituted amino group, or an amino- or substituted amino-alkyl group, e.g. where R_4 is

$$\begin{matrix} R_5 \\ >N—(CH_2)_n \\ R_6 \end{matrix}$$

wherein n=0—3 and R_5 and R_6 are hydrogen, C_1—C_6 alkyl or arylalkyl, or, together with the nitrogen atom may form a 5-, 6- or 7-membered ring which may or may not contain an additional hetero atom. Each of the aryl, aroyl or single ring aromatic heterocyclic groups represented by the radical Ar, and/or the aryl group represented by the radical R_3, may be substituted with from 1 to 3 identical or different groups chosen from the following: C_1—C_6-alkoxy, hydroxyl, amino, mono- or di-alkyl-substituted amino, nitro, fluoro, chloro or bromo, trifluoromethyl, C_1—C_6 straight or branched chain alkyl or sulphonamido. The single ring aromatic heterocyclic groups of the radical Ar may contain one or more hetero atoms and may, for example, be thiophene, pyridine or pyrimidine.

The radical R is a C_1—C_6 alkoxy or C_2—C_6 alkenoxy group, preferably a C_1—C_3 alkoxy group, and in particular a methoxy group. Examples of C_1—C_6 alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of C_2—C_6 alkenoxy groups are vinyloxy, propenoxy, butenoxy, pentenoxy and hexenoxy. Compounds in which R is the preferred methoxy group are specifically exemplified. The corresponding compounds in which R is the less preferred C_2—C_6 alkoxy or C_2—C_6 alkenoxy groups can readily be prepared in similar manner or by methods which, to the skilled person, are the obvious equivalents of those illustrated in detail in this specification.

The radical R_1 is preferably positioned at the 4 position of the aromatic ring. The corresponding compounds in which R_1 is in the less preferred 3 position can readily be prepared by analogous methods to those described in detail herein for the preferred 4-substituted compounds.

Although the radicals R_1 and R_2 are preferably different, they may also be the same (except in the case of hydrogen), and the compounds may be prepared by analogous methods in the two cases. Specific examples of the radicals R_1 and R_2 are: hydrogen; halogen, e.g. fluorine, chlorine or bromine; sulphonamido; amino; C_1—C_6 alkyl- or di-(C_1—C_6)-alkylamino, e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, or the corresponding dialkylamino groups in which the two alkyl radicals are the same or different; alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl; mono- or di-alkylsulphonamido, e.g. methylsulphonamido, ethylsulphonamido, propylsulphonamido or butylsulphonamido; or acylamino, e.g. formamido, acetamido, propionamido, butyramido, pentanamido or hexanamido, optionally substituted by up to 3 identical or different halogen atoms as, for example, in chloroacetamido or trifluoroacetamido, and optionally substituted by an amino or a mono- or dialkyl-amino group as, for example, in aminoacetamido or 1-piperidylacetamido, or ureido or N-alkylureido, e.g. N-methylureido or N-ethylureido. The radical R_1 is preferably amino, acetamido or substituted acetamido. R_2 is preferably hydrogen or chlorine. The corresponding compounds having the less preferred meanings for R_1 and R_2 can, of course, be prepared in a similar manner to the more preferred compounds, which are illustrated in detail below.

The radical R_3 may be hydrogen, C_1—C_6 alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl or hexyl) or aryl (e.g. phenyl or substituted phenyl). R_3 is preferably hydrogen, methyl or phenyl, and in particular hydrogen. Naturally, those compounds in which R_3 has the less preferred meanings can be prepared by similar methods to the preferred compounds, which are exemplified below, together with variations which would be obvious to a person skilled in the art.

The radical Ar may be aryl (e.g. phenyl), aroyl (e.g. benzoyl) or a single ring

aromatic heterocyclic group (e.g. thiophene, pyridine or pyrimidine). The radical Ar may also, of course, be substituted.

The number x is 0 or 1, preferably 0. Compounds in which x is the preferred 0 are specifically exemplified. The corresponding compounds in which x is the less preferred 1 can readily be prepared in similar manner or by methods which, to the skilled person, are the obvious equivalents of those illustrated in detail in this specification. Thus, for example, the N-containing 6- or 7-membered ring could be substituted with a cyano group, the cyano group reduced and the resulting amino group condensed with the appropriate aromatic acid chloride.

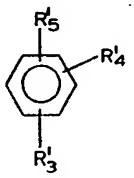
The number y is 2 or 3, preferably 2. The less preferred compounds in which y is 3 can, of course, be prepared by analogous methods to those described herein. Where y has the preferred value of 2, the bond from the $(CH_2)_x$ group preferably joins the piperidyl ring at the 4-position. The preparation of such compounds is exemplified below, but it will be apparent to the person skilled in the art that analogous methods could be used for the less preferred compounds.

The number z is an integer of from 1 to 6, preferably 1 to 3, and in particular 1. Once again, the person skilled in the art would recognise that the methods exemplified herein for the compounds in which z has the preferred values, may also be adapted, with minor and obvious modifications, to the preparation of compounds in which z has the less preferred values.

A preferred group of compounds includes N-aryl-alkyl piperidyl substituted benzamides which correspond to the general formula (I) wherein:

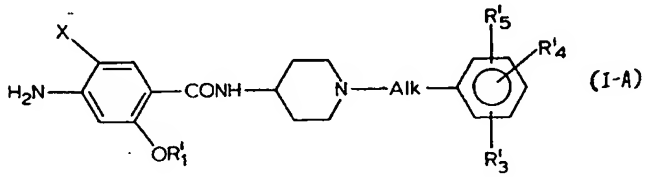
R_1 is NH_2 at the 4-position of the aromatic ring;
R_2 is chloro or bromo;
R is C_1—C_6 alkoxy or C_2—C_6 alkenoxy;
x is 0;
y is 2;

$-(CH)_z-$ is a straight chain alkylene or alkenylene residue containing up to six carbon atoms; or a C_1—C_6 alkyl-substituted methylene group; and
Ar is substituted aryl of the formula:



wherein R'_3, R'_4 and R'_5, which may be identical or different, are selected from hydrogen, halogen, C_1—C_6 alkoxy, hydroxy, nitro, amino, mono- or dialkylamino, trifluoromethyl, or together two of them may be methylene dioxy, in which case the third is hydrogen.

Therefore, this preferred group of compounds may be defined by the more specific formula (I—A):



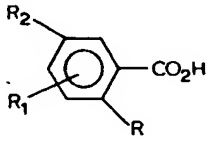
(I-A)

where
X is chloro or bromo;
R'_1 is C_1—C_6 alkyl or C_2—C_4 alkenyl;
Alk is a straight chain alkylene or alkenylene residue containing up to six carbon atoms; or a C_1—C_6 alkyl-substituted methylene group; and
R'_3, R'_4 and R'_5 are as hereinabove defined.

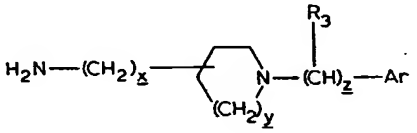
There preferred compounds may be described as N-[(1'-aryl-alkyl)-4'-piperidyl]-4-amino-5-halo-2-alkoxy or alkenoxy benzamides and derivatives thereof.

In another aspect of the invention, we provide a pharmaceutical composition, comprising a compound corresponding to the general formula (I), preferably (I—A), as defined above, together with a pharmacologically acceptable carrier or diluent.

The compounds of the invention may generally be prepared by reacting in an inert solvent the acid chloride of a substituted benzoic acid (II), where R, R_1 and R_2 have the same significance as above, with the appropriate N-heterocycle (III), where R_3, Ar. *x*, *y* and *z* have the same significance as above. The acid chloride of the acid (II) may be prepared by reacting the acid with an acid chloride, e.g., thionyl chloride, sulphonyl chloride, phosphoryl chloride or oxalyl chloride, in an inert solvent.



(II)



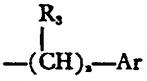
(III)

Compounds (I) may also be prepared by reacting the compound of structure (III) with a mixed anhydride of the substituted benzoic acid. The above reaction may be carried out in inert solvents at temperatures between ambient and 100° C. The mixed anhydride may be prepared *in situ*. At temperatures between −20 and +20° C, a monoalkyl ester of chloroformic acid, e.g. ethylchloroformate is added to the substituted benzoic acid (II) in the presence of a tertiary base, e.g. triethylamine or pyridine, in an inert solvent to form the mixed anhydride. To this reaction mixture with a temperature between −20 and +20° C the appropriate compound (III) is added.

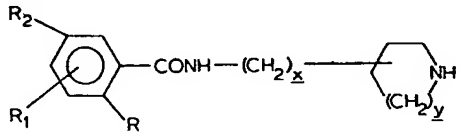
The inert solvents which may be used in the above reactions include aromatic hydrocarbons, alkylketones, alkylesters, alkylethers, cyclic ethers, such as tetrahydrofuran, and chlorinated hydrocarbons.

The free amino compounds (I) in which R_1 or $R_2=NH_2$ may be prepared from the corresponding acylamino derivative (I) in which R_1 or $R_2=R_4—CONH$, where $R_4=C_1—C_6$ alkyl, trifluoromethyl or α-monohalogenoalkyl, by hydrolysis in either an acidic or basic solution in solvents such as $C_1—C_6$ alcohols at temperatures between ambient and 100° C.

Compounds (I) in which R_3, *z* and Ar are as previously defined may also be prepared from the corresponding derivative of (I) in which the group

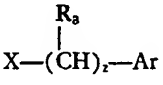


is replaced by hydrogen (Compound (IV)):



(IV)

The compound (IV) is prepared by subjecting the corresponding benzyl com-compound (I) in which $R_3=H$, $z=1$ and Ar=phenyl to catalytic hydrogenolysis in a solvent such as $C_1—C_6$ alcohol in the presence of a noble metal catalyst, e.g., palladium or platinum, which may be absorbed on an inert support such as carbon or barium sulphate, in the presence of hydrogen at normal or elevated pressure and at temperatures between ambient and 100° C. The compound (IV) may then be reacted with the appropriate halide of structure



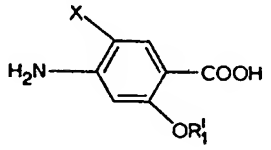
(where X=halogen), in the presence of a base such as sodium or potassium carbonate or sodium or potassium bicarbonate.

Amino acylamino compounds (I), where R_1 or R_2=R_4CONH in which R_4 is

$$\begin{matrix} R_5 \\ \\ R_6 \end{matrix} > N(CH_2)_n,$$

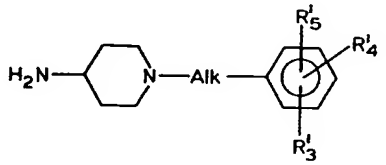
n, R_5 and R_6 having the same meaning as above, are prepared from the corresponding haloacyl derivative (R_4=halogen—$(CH_2)_n$) by reaction with the appropriate amine in an inert solvent, such as an aromatic or aliphatic hydrocarbon, chlorinated hydrocarbon or aliphatic or cycloaliphatic ether at temperatures between ambient and 100° C.

A compound of the general formula (I—A) as defined above, or a pharmaceutically acceptable salt thereof, may be prepared by reacting a 4-amino-5-halo benzoic acid of the formula:



(V)

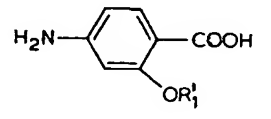
wherein X and R'_1 are as defined above,
or an active derivative thereof, the amino group optionally being protected, with a 4-amino-1-arylalkyl piperidine of the formula:



(VI)

wherein Alk, R'_3, R'_4 and R'_5 are as defined above, removing the protecting group where such a group is present; and optionally converting the product into a salt. The amino group may be protected with an acyl group such as acetyl, trifluoracetyl, chloracetyl or phthaloyl. The active derivative may be an ester, acid halide, mixed anhydride, N-imidazolide or azide. The reaction generally takes place in an inert solvent at a temperature of from −20 to 150° C, depending on the method of condensation used. When a 4-acylamino-5-halo-2-alkoxy benzoic acid is used, the desired compounds are liberated by acid hydrolysis of the acyl protecting group. For example, a 4-acetamido-5-halo-2-alkoxybenzoyl chloride may be reacted with 4-amino-1-benzyl piperidine in an inert solvent such as a halogenated hydrocarbon, an aromatic hydrocarbon, a C_1—C_6 alkyl ester of a C_1—C_6 alkanoic acid, a ketone or ether with C_1—C_6 alkyl groups, or a cyclic ether, such as tetrahydrofuran or dioxan, in the presence of an organic tertiary base such as, for example, pyridine or a triethylamine, to give the 4-acetamido derivative, which may then be hydrolysed in aqueous or aqueous-alcoholic acid solutions to yield a N-[(1′-benzyl)-4′-piperidyl]-4-amino-5-halo-2-alkoxy benzamide.

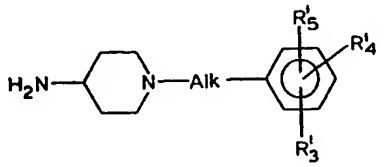
A compound of the formula (I—A) as defined above, or a pharmaceutically acceptable salt thereof, may also be prepared by reacting a 4-amino benzoic acid of the formula:



(VII)

wherein R'_1 is as defined above,

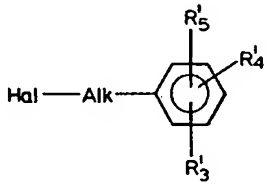
or an active derivative thereof, with a 4-amino-1-arylalkyl piperidine of the formula:



(VI)

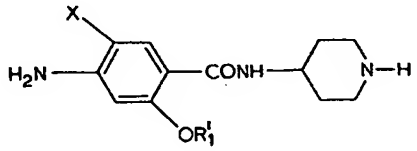
wherein Alk, R'_3, R'_4 and R'_5 are as defined above; chlorinating or brominating the resulting compound; and optionally converting the product into a salt.

In another embodiment, a compound of the formula (I—A) as defined above, or a pharmaceutically acceptable salt thereof, may be prepared by reacting an arylalkyl halide of the formula:



(VIII)

wherein Alk, R'_3, R'_4 and R'_5 are as defined above, and Hal is a halogen atom, with an N-[4′-piperidyl]-4-amino-5-halo benzamide of the formula:



(IX)

wherein X and R'_1 are as defined above,

or the 4-acyl derivative thereof; removing the 4-acyl group if present; and optionally converting the product into a salt. The reaction generally takes place in the presence of an inorganic or organic base in an inert solvent. The inert solvent may be an aromatic hydrocarbon, a C_1—C_6 alkyl ester of a C_1—C_6 alkanoic acid, a ketone or ether with C_1—C_6 alkyl groups, a cyclic ether, a C_1—C_6 alkyl cyanide or chlorinated hydrocarbon. The reaction may take place at temperatures between ambient and the boiling point of the solvent. As an inorganic base, potassium carbonate or sodium bicarbonate may be used.

For example, a 4-amino-5-halo-2-alkoxy benzoic acid may be converted into a mixed anhydride *in situ* with an alkyl chloroformate in the presence of a tertiary base, such as triethylamine or pyridine, in an inert solvent, such as a chlorinated hydrocarbon, a C_1—C_6 alkyl ester of a C_1—C_6 fatty acid, an alkyl ketone or ether with C_1—C_6 alkyl groups, a cyclic ether such as tetrahydrofuran or dioxan, at a temperature of from −20° C to room temperature; and the resulting mixed anhydride may then be reacted with 4-amino-1-benzyl piperidine to yield a N-[(1′-benzyl)-4′-piperidyl]-4-amino-5-halo-2-alkoxy benzamide. Such a compound may also be prepared by condensing the same acid or a 4-acylamino derivative thereof with 4-amino-1-benzyl piperidine in the presence of a dehydrating agent such as silicon tetrachloride, a mono-, di- or trialkyl silyl halide, titanium tetrachloride, dicyclohexylcarbodiimide, thionyl chloride or sulphur trioxide in dimethyl sulphoxide, toluene sulphonyl chloride, acetone dimethylacetal or a polymeric dehydrating agent. The reactions may be carried out in anhydrous inert solvents such as halogenated or aromatic hydrocarbons, pyridine, C_1—C_6 alkyl esters of C_1—C_6 alkanoic acids, alkyl ketones or ethers with C_1—C_6 alkyl groups, or cyclic ethers at temperatures between room temperature and the boiling point of the solvent used. If an acyl protecting group is present, the desired compounds are obtained by acid hydrolysis.

Preferred compounds according to the invention may also be prepared by condensing C_1—C_6 alkyl esters of 4-acylamino-5-halo-2-alkoxy benzoic acid with a 4-amino-1-arylalkyl piperidine of formula (VI) in an inert solvent, such as an aromatic or chlorinated hydrocarbon, in the presence of a base, such as an alkali metal C_1—C_6 alkoxide or a trialkoxy derivative of aluminium with continuous removal of the C_1—C_6 alcohol formed in the reaction.

Another example of a reactive derivative of a 4-amino or 4-acylamino-5-halo-benzoic acid of formula (V) which may be used is, for instance, the derivative formed from N-ethyl-5-phenylisoxazolinium 3-sulphonate (Woodwards Reagent).

The 4-amino-5-halo-benzoic acids (V) used as starting material for compounds (I—A) may be prepared from 4-acetamido salicyclic acid by alkylation and esterification of the 2-hydroxyl group and the acid group respectively by treatment with a C_1—C_6 alkyl halide or sulphate in an inert solvent, such as a C_1—C_6 alkyl ester of a C_1—C_6 alkanoic acid, an alkyl ketone with C_1—C_6 alkyl groups, in the presence of an inorganic base such as potassium carbonate. The product is then halogenated in the 5-position of the benzene nucleus with chlorine or bromine, in a solvent, such as acetic acid, in the presence of the halide of a heavy metal, such as iron chloride. Other halogenating agents, such as iodobenzene dichloride, may also be used. The corresponding acid may be prepared by acid hydrolysis in aqueous or aqueous alcoholic solutions.

4-Amino-1-arylalkyl piperidines of formula (VI) may be prepared by reduction of the corresponding 1-arylalkyl piperid-4-one oximes with alkali aluminium hydrides or alkali metals in an alcoholic solvent. [Harper N.J. et al, J. Med. Chem. 7, 729—732 (1964)].

The above mentioned 1-arylalkyl 4-piperidone oximes may be prepared by reaction of the corresponding ketone with hydroxylamine hydrochloride in an aqueous alcoholic solution. The 1-aryl-alkyl-4-piperidones are prepared by known procedures [e.g., Beckett et al J. Med. Pharm. Chem. *1*, 37 (1959)] or from 4-piperidone hydrochloride. The latter compound is converted into its diethylene ketal with ethylene glycol. The ketal is then reacted with an aryl or arylalkyl acid halide to yield a 1-aroyl or 1-aryl-alkoyl piperidone ethylene ketal which may be reduced with lithium aluminium hydride to give the corresponding 1-arylalkyl piperidone diethylene ketal, acid hydrolysis of which yields the 1-arylalkyl-4-piperidone.

The N-oxide derivatives of the compounds of formula (I) may be prepared by known procedures.

The invention also provides salts of compounds of structures (I), preferably (I—A), with biologically and pharmacologically acceptable inorganic and organic acids, non-limiting examples of which are sulphates; hydrohalide salts; phosphates; C_1—C_6 alkane sulphonates; arylsulphonates; salts of C_1—C_{20} aliphatic mono-, di- or tribasic acids which may contain one or more double bonds, an aryl nucleus or other functional groups such as hydroxy, amino, or keto; salts of aromatic acids in which the aromatic nuclei may or may not be substituted with groups such as hydroxyl, C_1—C_6 alkoxy, amino, mono- or di- (C_1—C_6)-alkylamino, sulphonamido. Also included within the scope of the invention are quaternary salts of the tertiary nitrogen atom with C_1—C_6 alkyl halides or sulphates, and N-oxide derivatives of the tertiary nitrogen atom. In preparing dosage formulations, those skilled in the art will select the pharmaceutically acceptable salts.

Compositions of the active compounds with pharmaceutically acceptable ingredients for oral and parenteral routes of administration are also included in the invention. The pharmaceutically acceptable diluents or carriers which are admixed with the active compound, or compounds, or salts of such compounds, to form the compositions of this invention are well known *per se* and the actual excipients used depend *inter alia* on the method of administering the compositions. The compositions of this invention may be adapted for oral, topical, percutaneous or parenteral use but the preferred method of administration is *per os*. In this case, the oral compositions may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredients, together with colouring or flavouring if desired. Tablets or capsules may conveniently contain between 0.1 and 20 mgs and preferably from 0.1 to 5 mgs of active component or the equivalent amount of its salts.

The liquid compositions adapted for oral use may be in the form of solutions or

suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or its salt or derivative in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

In another aspect of the invention, the compounds may be mixed with other active anti-acid and anti-ulcer agents (excluding anticholinergic agents) for oral or in appropriate cases for parenteral use.

The compounds cases of the present invention have exhibited activities which may be considered beneficial in the treatment of gastrointestinal and cerebral malfunction in mammals including animals and man. The characteristic properties of these compounds are an antagonism of the effects of the dopaminergic agent, apomorphine, in animals, local anaesthetic activity and the ability to induce catatonia in rats and mice. Consequently, they may be useful in the treatment of nausea and vomiting of diverse origin and as neuroleptic or tranquillizing agents.

Compounds provided by this invention have been shown to have antiemetic and neuroleptic properties and to increase the rate of stomach emptying in man. For example the compounds of formula (I—A) have exhibited such properties at single doses of between 0.01 (10 μg) and 20 mg. They may be used in doses of from 0.1 to 1000 mg per day for the treatment of nausea and vomiting due to gastrointestinal disorders, congestive heart failure, post operative conditions, other gastrointestinal tract disorders such as dyspepsia, flatulance, bile regurgitations, hiatus hernia, peptic ulcer, reflex oesophagitis, gastritis, duodenitis and cholelithiasis, and as an adjunt to radiography of the gastrointestinal tract, or may be used as neuroleptic or tranquillizing agents. The compounds cause considerably less disturbance in the central nervous system than does chlorpromazine or other phenothiazine anti-emetic agents, probably as a function of their more selective anti-dopaminergic effects.

Standard pharmacological tests have been run using many of the compounds defined by the generic structural formulae (I), preferably (I—A). These tests have been run with rats, mice, dogs and humans. In many of these tests, the compounds of the invention have been compared with metoclopramide and other known therapeutic compounds which have properties similar to those compounds of the present invention.

A number of the compounds of the present invention were screened in parallel with metoclopramide for potential anti-emetic effects against apomorphine-induced gnawing in the rat and as local anaesthetics on the rat sciatic nerve (Table I). The most active compounds were also tested for their ability to decrease gastric emptying time in rats.

As can be seen from Table I, some of these compounds exhibit a similar profile of activity to metoclopramide and, in particular, compounds Nos. 2, 7 and 8 are more active as anti-emetics. Some of the compounds do not exhibit anti-apomorphine activity in rats even at high doses, but are active in antagonising the effect of apomorphine in dogs and in pidgeons at doses of 10—100 μg/Kg and 10—50 mg/Kg respectively. Examples of such compounds are given by formula (I) where

$R=OCH_3$, $R_1=H$, $R_2=SO_2NEt_2$, $x=O$, $y=2$, $R_3=H$, $z=1$, $Ar=C_6H_5$; and

$R=OCH_3$, $R_1=H$, $R_2=SO_2C_2H_5$, $x=O$, $y=2$, $R_3=H$, $z=1$, $Ar=C_6H_5$.

The compounds cause considerably less disturbance in the central nervous system than does chlorpromazine and other phenothiazine anti-emetic agents.

TABLE I

FORMULA I

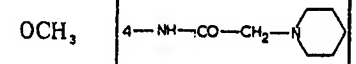
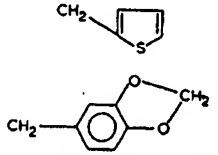
No.	R	R_1	R_2	x	y	R_3 / $-(CH)_z-Ar$	* Antiapomorphine in rat	Local Anaes. (1%)	Catatonia rats
1	OCH_3	4-NHCO–CH_3	Cl	0	2	$CH_2-C_6H_5$	+++	+	+
2	OCH_3	4-NH–CO–CH_2–Cl	Cl	0	2	$CH_2-C_6H_5$	++++	–	+
3	OCH_3		Cl	0	2	$CH_2-C_6H_5$	+++	+	+
4	OCH_3	4-NH–CO–CH_2–Cl	H	0	2	$CH_2-C_6H_5$	++	+	+
5	OC_2H_5	4-NH–CO–CH_2–Cl	H	0	2	$CH_2-C_6H_5$	+	+	N. t.
6	OCH_3	4-NH–CO–CF_3	H	0	2	$CH_2-C_6H_5$	++	–	+
7	OCH_3	4-NH_2	H	0	2	$CH_2-C_6H_5$	++++	+	N. t.
8	OCH_3	4-NH–CO–CF_3	Cl	0	2	$CH_2-C_6H_5$	+++++	+	+
9	OCH_3	H	Cl	0	2	$CH_2-C_6H_5$	+	+	+
10	OCH_3	4-NH_2	Cl	1	2	$CH_2-C_6H_5$	++	+	N. t.
11	OCH_3	4-NH_2	Cl	0	2	$CH_2-C_6H_4$–3-OCH_3	++	+	+
12	OCH_3	4-NH_2	Cl	0	2		+++	+	+
13	OCH_3	4-NH_2	Cl	0	2	$CH_2CH=CH-C_6H_5$	++	+	+

TABLE I (Continued)

FORMULA I

No.	R	R_1	R_2	x	y	R_3 | $-(CH)_z-Ar$	* Antiapomorphine in rat	Local Anaes. (1%)	Catatonia rats
14	OCH_3	4-NH_2	Cl	0	2	$CH=(C_6H_5)_2$	+	+	N. t.
15	OCH_3	4-NH_2	Cl	0	2	$CH_2C_6H_4$-2-OCH_3	++	+	N. t.
16	OCH_3	4-NH_2	Cl	0	2	$CH_2C_6H_4$-2-Cl	++	+	N. t.
METOCLOPRAMIDE							+++	+	+
CHLORPROMAZINE							++++	+	+

* Antiapomorphine activity in rats scored as follows :

\+ active at 50 mg/Kg

++ active at 25 mg/Kg

+++ active at 12.5 mg/Kg

++++ active at 6.25 mg/Kg

+++++ active at.3.125 mg/Kg

A number of the compounds of the invention have been extensively tested in humans to determine maximum dosages and the therapeutic effects of the compounds. These compounds have been administered to humans orally and parenterally.

The following Examples illustrate the preparation of various compounds of the present invention (including starting materials therefor).

EXAMPLE 1.

2-methoxy-4-(α,α,α-trifluoroacetamido)-5-chloro-benzoic acid.

2.65 g (0.037 mol) of chlorine dissolved in 50 ml of acetic acid were added to a suspension of 9 g (0.034 mol) of 2-methoxy-4-(α,α,α-trifluoroacetamido) benzoic acid in 160 ml acetic acid, slowly maintaining the temperature between 15—20° C.

At the end of the addition the reaction mixture was kept at ambient temperature for 4 hours. The reaction mixture was then poured into ice-water when a white solid was precipitated, and was filtered and dried. It was then crystallized from acetone-diethyl ether to give 9.1 g of crystals, m.p. 178—180° C yield 90%. Using the same procedure, the following acids were also obtained: 2-methoxy-4-acetamido-5-chlorobenzoic acid—m.p. 208—210° C, 2-methoxy-4-(α-chloro acetamido)-5-chlorobenzoic acid—m.p. 183—185° C.

EXAMPLE 2.

2-methoxy-4-(α,α,α-trifluoroacetamido)-5-chloro benzoyl chloride.

A mixture of 10 g (0.033 mol) of 2-methoxy-4-(α,α,α-trifluoroacetamido)-5-chloro benzoic acid, 6.6 ml. of thionyl chloride and 15 ml of dry benzene was heated at 60—70° C for 4 hours. The resulting solution was poured into 50 ml of petroleum ether and the precipitated product was collected by filtration in the form of a colourless solid (9 g) m.p. 91—93° C. By the same precedure the following acid chlorides were obtained: 2-methoxy-4-acetamido-5-chlorobenzoyl chloride—m.p. 144—145° C, and 2-methoxy-4-(α-chloroacetamido)-5-chlorobenzoyl chloride—m.p. 123—125° C.

EXAMPLE 3.

N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(α,α,α-trifluoroacetamido)-5-chlorobenzamide hydrochloride.

A solution of 14.7 g (0.046 mol) of 2-methoxy-4-(α,α,α-trifluoroacetamido)-5-chlorobenzoyl chloride in 100 ml of methyl ethylketone was added slowly, maintaining the temperature at 0—5° C, to a solution of 7.99 g (0.042 mol) of 1-benzyl-4-amino piperidine in 75 ml of methyl ethyl ketone cooled to a temperature of 0—5° C. After the addition had been completed, the reaction mixture was maintained at the same temperature with stirring for 1 hour and finally at room temperature for 5 hours.

The solid which had precipitated was filtered, washed with methyl ethyl ketone and then crystallized from ethanol to give 20 g of a white solid, m.p. 227—228° C. By the same procedure the following compounds were prepared: N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-acetamido-5-chlorobenzamide—m.p. 134—135° C; N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(α-chloroacetamido)-5-chlorobenzamide hydrochloride monohydrate—m.p. 178—180° C; and N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-α-chloroacetamido-benzamide hydrochloride—m.p. 245—246° C.

EXAMPLE 4.

N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(α,α,α-trifluoroacetamido) benzamide hydrochloride.

A solution 19.7 g (0.075 mol) of 2-methoxy-4-(α,α,α-trifluoroacetamido) benzoic acid in 150 ml of dry tetrahydrofuran was cooled to -15 to -10° C.

10.52 ml (0.075 mol) of triethylamine in 30 ml of dry tetrahydrofuran was slowly added, followed by 7.05 ml (0.075 mol) of ethyl chloroformate, also dissolved in dry tetrahydrofuran.

Stirring was maintained for 1 hour at -15 to -10° C and then 14.26 g (0.075 mol) of 1-benzyl-4-amino piperidine in 30 ml of tetrahydrofuran was added. The temperature of the reaction was allowed to reach ambient temperature with agitation and was maintained at this temperature for 6 hours, at the end of which the precipitate was filtered. The organic extracts were concentrated at low temperature, the residue was dissolved in chloroform and the solution was washed several times with water.

The chloroform extracts were concentrated at low temperature to yield a paste which was dissolved in warm diethyl ether and allowed to crystallize, when a white solid, 27 g m.p. 183—185° C, was obtained. This material was dissolved in acetone

and a saturated solution of hydrochloric acid in ethanol was added to give a slightly acid solution. The precipitated hydrochloride salt was recrystallized from methanol to give 28 g of the hydrochloride, m.p. 239° C (d). By the same procedure the following were obtained: N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-5-chlorobenzamide hydrochloride—m.p. 236—238° C; and N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-5-sulphamoyl-benzamide hydrochloride—m.p. 175—178° C.

EXAMPLE 5.

N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-aminobenzamide dihydrochloride.

50 ml of NaOH (8N) were added to a solution of 13.93 g (0.032 mol) of N-[(1'-benzyl)-4'-piperidyl] 2-methpxy-4-(α,α,α-trifluoroacetamido) benzamide in 50 ml of ethanol, and the reaction mixture was stirred at ambient temperature for 3 hours, at the end of which time it was diluted with water and was extracted with chloroform. The chloroform extracts were dried, decolorized and concentrated at low temperature to give a residue which was dissolved in acetone. A saturated solution of HCl in ethanol was added to the acetone solution until the solution was slightly acid. The solid was collected and recrystallized from ethanol to give 12 g of a white product, m.p. 215—217° C (d).

EXAMPLE 6.

N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(N'-methylureido) benzamide hydrochloride.

6 g (0.017 mol) of N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-aminobenzamide dissolved in 30 ml of acetone-diethyl ether was stirred at room temperature while 2.56 ml, 0.034 mol) of methyl isocyanate in 10 ml of diethyl ether was added. The resultant reaction mixture was stirred at ambient temperature for 6 hours. The resulting white precipitate was filtered to give 5.5 g m.p. 185—187° C. It was then converted to the hydrochloride which was crystallized from methanol to give a colourless solid (5.5 g) m.p. 239—241° C (d).

EXAMPLE 7.

N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(methylsulphonamido) benzamide hydrochloride.

1.05 ml (0.0132 mol) of methansulphonylchloride in 10 ml of dry benzene were slowly added to a solution of 4.2 g (0.012 mol) of N-[(1'-benzyl)-4'-piperidyl] 2-methoxy-4-amino benzamide in 50 ml of dry benzene. The reaction mixture was stirred at ambient temperature for 4 hours, at the end of which time the precipitate was filtered and crystallized from ethanol to give 5.3 g of pure product, m.p. 235—237° C.

EXAMPLE 8.

N-[(1'-benzyl)14'-piperidyl)-2-methoxy-4-α-(1''-piperidyl) acetamido-5-chlorobenzamide dihydrochloride.

A mixture of 11 g (0.0244 mol) of N-[(1'-benzyl)-4'-piperidyl]-2-methoxy-4-(α-chloroacetamido)-5-chlorobenzamide and 5.07 ml (0.0512 mol) of piperidine in 50 ml of dry benzene was refluxed for 12 hours. At the end of the reaction, the product was filtered and washed several times with benzene. The benzene extracts were washed with water, decolourized, dried and concentrated at low temperature to give a paste. The latter was dissolved in a mixture of warm diethyl ether-petroleum ether and allowed to crystallize when a white solid was obtained, m.p. 135—137° C. It was converted into the dihydrochloride in the usual manner, crystallizing from ethanol-acetone to give 11 g of product, m.p. 241—243° C.

EXAMPLE 9.

N-(4'-piperidyl) 2-methoxy-4-acetamido-5-chlorobenzamide hydrochloride.

A solution of 10 g (0.022 mol) of N-[(1'-benzyl)-4'-piperidyl 2-methoxy-4-acetamido-5-chlorobenzamide hydrochloride in 100 ml of ethanol was agitated with hydrogen at ambient temperature and atmospheric pressure in the presence of 1 g of Pd/C. (10%). After 8 hours the theoretical quantity of hydrogen had been absorbed, the catalyst was filtered and the filtrate was evaporated to dryness. The residue was crystallized from methanol-acetone and finally from ethanol to give 7 g of product, m.p. 228—230° C. The following compounds were prepared by the same procedure: N-(4'-piperidyl)-2-methoxy-4-amino-5-chlorobenzamide—m.p. 168—170° C and N-(4'-piperidyl)-2-methoxy-5-sulphamoylbenzamide hydrochloride m.p. 249—250° C.

EXAMPLE 10.

N-[(1'-(3"p-fluorobenzoyl)propyl)-4'-piperidyl]-2-methoxy-4-acetamido-5-chlorobenzamide hydrochloride.

A mixture of 4 g (0.0122 mol) of N-(4'-piperidyl)-2-methoxy-4-acetamido-5-chlorobenzamide, 2.695 g (0.0134 mol) of 4-chloro- *p*-fluorobutyrophenone, 1,134 g (0.0135 mol) of sodium bicarbonate, a crystal of potassium iodide and 70 ml of dry toluene was refluxed for 3 days, at the end of which time the inorganic products were filtered and washed with chloroform. The organic extracts were evaporated at low temperature to give a residue which was dissolved in acetone and converted to the hydrochloride by addition of HCl in ethanol. The product was crystallized from methanol to give 4.5 g, m.p. 195—197° C. By the same procedure the following product was also obtained: N-[(1'-phenylethyl)-4'-piperidyl]-2-methoxy-4-acetamido-5-chlorobenzamide hydrochloride, m.p. 222—223° C.

EXAMPLE 11.

4-acetamidosalicyclic acid.

30.6 g (0.2 mol) *p*-aminosalicyclic acid and 100 cc ethanol were introduced into a 250 ml flask, and the mixture was heated to 40° C. 20.4 g (0.2 mol) acetic anhydride was then added at such a rate that the temperature did not exceed 50° C. When the addition was complete, the mixture was stirred at 50° C for 3 hours. The product was filtered. Weight: 36 g, b.p.=235° C. Yield=92%.

EXAMPLE 12.

Methyl 2-methoxy-4-acetamidobenzoate.

34 g (0.17 mol) 4-acetamidosalicyclic acid, 57.96 g (0.42 mol) K_2CO_3 and 250 ml acetone were introduced into a 500 cc flask and heated to 40° C. Then, maintaining the same temperature, 51.40 g (0.408 mol) methyl sulphate was added in approximately 15 minutes, and the mixture was heated under reflux for 5 hours. The mixture was cooled, the K_2SO_4 precipitate was filtered and the acetone solution was concentrated to 1/3 of its original volume. Dilution with ethyl ether gave a crystalline solid which was filtered. weight 34 g, m.p.=130—131° C. Yield=89%.

EXAMPLE 13.

Methyl 2-methoxy-4-acetamido-5-chlorobenzoate.

34.8 g methyl 2-methoxy-4-acetamidobenzoate, 180 ml acetic acid and a trace of $FeCl_3$ were introduced into a 500 cc flask, provided with an agitator, a thermometer and a gas inlet. The solids were dissolved by heating and the solution was cooled to 15° C. Maintaining this temperature, a current of chlorine was passed through the solution, the reaction being controlled by cooling, until the weight had increased by 11.2 g. The solution obtained was poured into 2 litres of water, precipitating a white solid, which was filtered to yield 33 g of product. m.p.=149—152° C. Yield=82%.

EXAMPLE 14.

2-methoxy-4-amino-5-chloro benzoic acid.

25.75 g (0.1 mol) methyl 2-methoxy-4-acetamido-5-chlorobenzoate suspended in 100 ml ethanol, were introduced into a 500 ml flask. 40 g NaOH, dissolved in 150 cc of water, were added and the mixture was heated under reflux for 2.5 hours. The mixture was diluted with water and made acid with concentrated HCl. The white solid which precipitated was collected and recrystallized from methanol. Weight: 17 g m.p.=213—215° C. Yield=84%.

EXAMPLE 15.

1-benzyl-4-piperidone-oxime.

48 g 1-benzyl-4-piperidone oxime hydrochloride (1) were placed in a liquid-liquid extraction apparatus, and dissolved in a solution of 8 grs NaOH in 100 ml water. After 7 hours of extraction with diethyl ether, 38 g white solid were obtained. m.p.=129—131° C. Yield=93%.

(1) P. Brookers, R. J. Terry and Walker. J. Chem. Soc. 3172 (1957).

EXAMPLE 16.

1-benzyl-4-amino-piperidine.

7.6 g (0.2 mol) lithium aluminium hydride and 300 ml anhydrous diethyl ether were introduced into a 1 l. flask, provided with a mechanical agitator and a Soxhlet extractor. 20 g (0.1 mol) 1-benzyl-4-piperidone oxime were placed in the Soxhlet

cartridge, and the mixture was heated under reflux for 12 hours, at the end of which time the excess of $LiAlH_4$ was destroyed. The ethereal extracts were dried and concentrated to dryness giving an oil that weighed 18 g. On distillation *in vacuo* 17 g of pure product were obtained. b.p.=103—105° C at 0.07 mm Hg.

By a similar procedure the following compounds were prepared:

1-phenethyl-4-aminopiperidine dihydrochloride, m.p. 333—335° C;
1(*m*-methoxybenzyl)-4-aminopiperidine dihydrochloride, m.p. 240—242° C;
1(*p*-methoxybenzyl)-4-aminopiperidine dihydrochloride, m.p. 257—259° C;
1(*m*-chlorobenzyl)-4-aminopiperidine dihydrochloride, m.p. 275—276° C;
1(*p*-chlorobenzyl)-4-aminopiperidine dihydrochloride, m.p. 308—310° C;
1-cinnamyl-4-amino-piperidine, b.p. 106—108/0.04 mm Hg;
1-piperonyl-4-amino-piperidine, m.p. 52—53° C;
1-(2'-thenyl)-4-amino-piperidine dihydrochloride, m.p. 259—261° C;
1(*o*-chlorobenzyl)-4-aminopiperidine dihydrochloride, m.p. 248—250° C;
1(3',4'-dichlorobenzyl)-4-aminopiperidine dihydrochloride, m.p. 288—291° C;
1(*o*-methoxybenzyl)-4-aminopiperidine dihydrochloride, m.p. 224—225° C;
1(dephenyl-methyl)-4-aminopiperidine, m.p. 88—92° C;
1(3',4'-dimethoxybenzyl)-4-aminopiperidine dihydrochloride, m.p. 229—231° C;
1(3',4',5'-trimethoxybenzyl)-4-aminopiperidine, m.p. 42—45° C;
1(1-phenylethyl)-4-aminopiperidine dihydrochloride, m.p. 275—277° C; and
1(2'-methoxy-5'-chlorobenzyl)-4-aminopiperidine dihydrochloride m.p. 255—59° C (d).

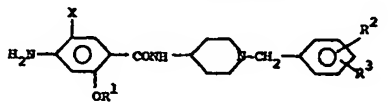
EXAMPLE 17.

By procedures similar to those described in Example 3 of the Complete Specification of our Applications Nos. 25537/77 and 25538/77 (Serial No. 1,507,463) divided from the present application, the following compounds were prepared using starting materials mentioned in Example 16 above:

N - [(1' - phenethyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p.=243—245° C;
N - [(1' - m - methoxy - benzyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5-chlorobenzamide hydrochloride, m.p.=226—227° C;
N - [(1' - cinnamyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p.=231—233' C;
N - [(1' - [2" - thenyl]) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p.=231—233° C;
N - [(1' - diphenyl - methyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5-chloro - benzamide, m.p.=153—159° C;
N - [(1' - *o* - methoxy - benzyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5-chloro - benzamide hydrochloride monohydrate,m.p.=166—168° C;
N - [(1' - *o* - chlorobenzyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5-chloro - benzamide hydrochloride, m.p.=221—224° C;
N - [(1' - [3",4" - dichlorobenzyl]) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5-chloro - benzamide hydrochloride, m.p.=212—214° C;
N - [(1' - [3",4",5" - trimethoxy - benxyl]) - 4' - piperidyl] - 2 - methoxy - 4-amino - 5 - chloro - benzamide, m.p.=80—82° C;
N - [(1' - [3",4" - dimethoxy - benzyl[) - 4' - piperidyl] - 2 - methoxy - 4 - amino-5 - chloro - benzamide, m.p.=175—178° C;
N - [(1' - 1 - phenylethyl) - 4' - piperidyl] - 2 - methoxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p.=247—250° C; and
N - [(1' - benzyl) - 4' - piperidyl] - 2 - methoxy - 5 - methylsulphonyl - benzamide hydrochloride, m.p.=206—208° C. (d).

Pharmaceutical compositions incorporating compounds of general formula (I), preferably (I—A), e.g. those described in the foregoing Examples, or pharmaceutically acceptable salts thereof, may be formulated substantially as described in Examples 6 to 13 of the Complete Specification of Application Nos. 25537/77 and 25538/77 but using instead of a salt of N-(1-benzylpiperid-4-yl)-2-methoxy-4-amino-5-chlorobenzamide as active ingredient a similar salt of a compound of the present invention conforming to general formula (I), preferably (I—A).

In the Complete Specification of our Applications Nos. 25537/77 and 25538/77 (Serial No. 1,507,463) (divided from the present application) we have described and claimed N-(1-benzylpiperid-4-yl)-benzamides of the general formula:—



(X)

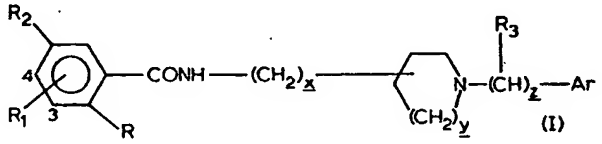
wherein X represents a chlorine or bromine atom, R^1 represents a straight- or branched-chain alkyl group containing up to six carbon atoms, R^2 and R^3 represent hydrogen atoms, or one of those symbols represents a chlorine atom in the 3- or 4-position or a methyl or methoxy group in the 4-position and the other symbol represents a hydrogen atom, or R^2 and R^3 together represent a methylenedioxy group attached to the 3- and 4-positions, and pharmaceutically acceptable salts thereof.

We make no claim in this application to benzamide derivatives of general formula (X) or pharmaceutically acceptable salts thereof, or N-oxide derivatives thereof, to any method for their preparation or to pharmaceutical compositions containing them.

Subject to the foregoing disclaimer:—

WHAT WE CLAIM IS:—

1. A compound corresponding to the general formula (I):



(I)

in which:

R is a C_1—C_6 alkoxy or C_2—C_6 alkenoxy group;

R_1 and R_2, which may be the same or different, are chosen from hydrogen (provided that R_1 and R_2 are not both hydrogen), halogen, sulphonamido, amino, (C_1—C_6)-alkyl- or di-(C_1—C_6)-alkylamino, alkylsulphonyl, mono- or di-alkylsulphonamido or acylamino groups, the radical R_1 being positioned at the 3 or 4 position of the aromatic ring;

R_3 is hydrogen, a C_1—C_6 alkyl or optionally substituted aryl group, provided that, where z is greater than 1, R_3 is hydrogen or two groups R_3 on adjacent C-atoms form a bond between the said C-atoms with any remaining groups R_3 being hydrogen;

Ar is an optionally substituted aryl, aroyl or single ring aromatic heterocyclic group;

x is 0 or 1;

y is 2 or 3; and

z is an integer of from 1 to 6,

or a pharmaceutically acceptable salt or N-oxide derivative thereof.

2. A compound according to claim 1, wherein the acylamino group which may be the radical R_1 and/or R_2 is represented by the formula:

$$R_4CO.NH$$

where R_4 is hydrogen, C_1—C_6 alkyl, mono- di-, or tri-substituted halogenoalkyl, an amino or substituted amino group, or an amino- or substituted amino-alkyl group.

3. A compound according to claim 2, wherein R_4 is represented by the formula:

$$\begin{matrix} R_5 \\ \\ R_6 \end{matrix}\!\!>\!N\!-\!(CH_2)_n\!-$$

where n is 0, 1, 2 or 3; and

R_5 and R_6 may each be hydrogen, C_1—C_6 alkyl or arylalkyl, or, together with the nitrogen atom, may form a 5-, 6- or 7-membered ring optionally containing an additional hetero atom.

4. A compound according to any of claims 1 to 3, wherein the aryl, aroyl or single ring aromatic heterocyclic group represented by the radical Ar, and/or the aryl group represented by the radical R_3, is substituted with from 1 to 3 identical or different

groups chosen from C_1—C_6-alkoxy, hydroxyl, amino, mono- or di-alkyl-substituted amino, nitro, fluorine, chlorine, bromine, trifluoromethyl, C_1—C_6 straight or branched chain alkyl or sulphonamido.

5. A compound according to any of claims 1 to 4, wherein the single ring aromatic heterocyclic group which may be radical Ar is thioprene, pyridine or pyrimidine.

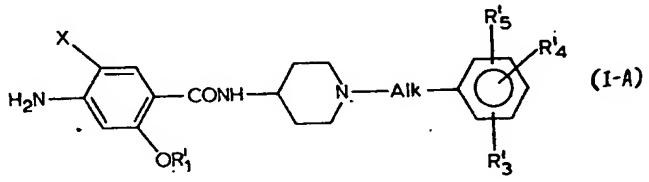
6. A compound according to any of claims 1 to 5, wherein x is 0.

7. A compound according to any of claims 1 to 6, wherein y is 2 and the bond from the $(CH_2)_x$ group joins the piperidyl ring at the 4-position.

8. A compound according to any of claims 1 to 7, wherein z is from 1 to 3.

9. A compound according to any of claims 1 to 8, wherein z is 1.

10. A compound according to claim 1 and corresponding to the general formula (I—A):



(I-A)

wherein

X is chloro or bromo;

R'_1 is C_1—C_6 alkyl or C_2—C_6 alkenyl;

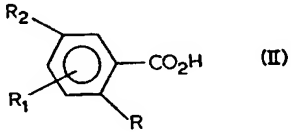
Alk is a straight chain alkylene or alkenylene residue containing up to six carbon atoms or a C_1—C_6 alkyl-substituted methylene group; and

R'_3, R'_4 and R'_5, which may be identical or different, are each hydrogen, halogen, C_1—C_6 alkoxy, hydroxy, nitro, amino, mono- or dialkylamino, trifluoromethyl or together two of them may be methylene dioxy, in which case the third is hydrogen, or a pharmaceutically acceptable salt or N-oxide derivative thereof.

11. A compound according to any of claims 1 to 10, wherein the pharmaceutically acceptable salt is the malate or hydrochloride.

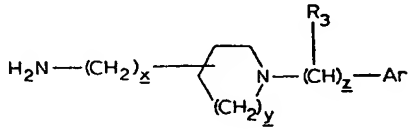
12. A compound corresponding to the general formula (I) as defined in claim 1 and named in any of the specific Examples 3 to 10 and 17.

13. A method of preparing a compound corresponding to the general formula (I), or a pharmaceutically acceptable salt thereof, which comprises reacting an acid chloride or mixed anhydride of a substituted benzoic acid corresponding to the general formula (II):



(II)

with a compound corresponding to the general formula (III):



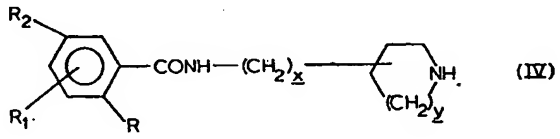
(III)

the radicals R, R_1, R_2, R_3, Ar and the numbers x, y and z having the meaning as defined in claim 1, and optionally converting the resulting product into a salt.

14. A method of preparing a compound corresponding to the general formula (I), substantially as herein described with reference to any of the specific Examples 3 to 10 and 17.

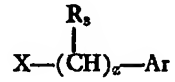
15. A process for the preparation of a compound of the formula (I) as defined

in claim 1, which comprises subjecting a compound (I) in which R_3=H, z=1 and Ar=phenyl to catalytic hydrogenolysis; and reacting the resulting compound (IV):



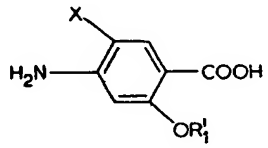
(IV)

with a halide of the formula:

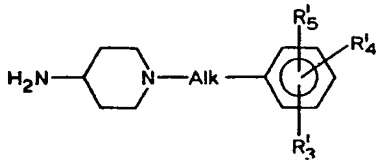


where X=halogen, in the presence of a base.

16. A process for the preparation of a compound of the general formula (I—A) as defined in claim 10, or a pharmaceutically acceptable salt thereof, which comprises reacting a 4-amino-5-halo benzoic acid of the formula:

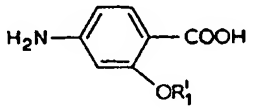


wherein X and R'_1 are as defined in claim 10,
or an active derivative thereof, the amino group optionally being protected, with a 4-amino-1-arylalkyl piperidine of the formula:

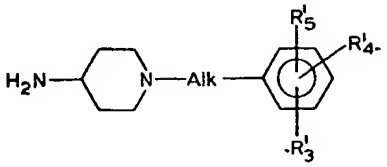


wherein Alk, R'_3, R'_4 and R'_5 are as defined in claim 10; removing the protecting group where such a group is present; and optionally converting the product into a salt.

17. A process for the preparation of a compound of the formula (I—A) as defined in claim 10, or a pharmaceutically acceptable salt thereof, which comprises reacting a 4-amino benzoic acid of the formula:

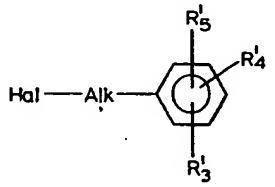


wherein R'_1 is as defined in claim 10, or an active derivative thereof, with a 4-amino-1-arylalkyl piperidine of the formula:



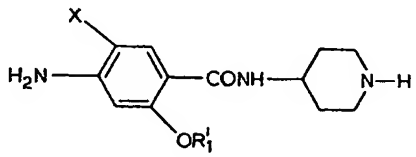
wherein Alk, R'_3, R'_4 and R'_5 are as defined in claim 10; clorinating or brominating the resulting compound; and optionally converting the product into a salt.

18. A process for the preparation of a compound of the formula (I—A) as defined in claim 10, or a pharmaceutically acceptable salt thereof, which comprises reacting an arylalkyl halide of the formula:



wherein Alk, R'_3, R'_4 and R'_5 are as defined in claim 10, and Hal is a halogen atom,

with an N-[4'-piperidyl]-4-amino-5-halo benzamide of the formula:



wherein X and R'_1 are as defined in claim 10;

or the 4-acyl derivative thereof; removing the 4-acyl group if present; and optionally converting the product into a salt.

19. A process according to any of claims 16 to 18, substantially as herein described.

20. A compound of the general formula (I) when prepared by a process according to any of claims 13 to 19.

21. A pharmaceutical composition comprising a compound of the general formula (I) and a non-toxic pharmacologically acceptable carrier or diluent therefor.

22. A pharmaceutical composition comprising a compound of the general formula (I—A) and a non-toxic, pharmacologically acceptable carrier or diluent thereof.

23. A pharmaceutical composition according to claim 21 or 22, also containing at least one other anti-acid or anti-ulcer agent (excluding anticholinergic agents).

24. A pharmaceutical composition according to claim 21 or 22 substantially as herein described.

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